REMARKS

A. Rejection Under 35 U.S.C. § 102(b) over Baksh et al. (WO 02/086104; U.S. 2004/0137612), herein "Baksh."

On page 2 of the Office Action, claims 1-3, and 8-16 remain rejected under 35 U.S.C. § 102(b) over Baksh. Applicants respectfully traverse the rejection.

The grounds for maintaining the rejection are as follows.

> Contrary to Applicant's assertions Baksh et al. teach the following at ¶ [0079]. [F]or differentiation into chondroblasts, the progenitors can be grown in serum-free DMEM supplemented with TGF-beta in suspension culture, for about 14 days or more. This passage clearly teaches the use of non-static conditions in a serum-free culture of progenitor cells, and therefore reads on claims 1-3 and 8-11.

Applicants respectfully disagree with the Examiner's conclusion about what this passage clearly teaches.

Cited Protocol Uses Static Culture

The Examiner is respectfully referred to the attached Declaration of one of the inventors, Dr. Dolores Baksh. In this Declaration, Dr. Baksh explains what the conditions of the cited protocol would have been. She explains how this protocol would not have been conducted under non-static culture conditions. The Examiner is specifically referred to pages 3-4 of Dr. Baksh's Declaration.

On the other hand, the claims are limited to a method in which cells are cultured under non-static conditions. Therefore, Applicants respectfully submit that the cited protocol does not anticipate the claims.

Progenitor Cells Not Expanded in Serum-Deprived Medium

The cited protocol fails to anticipate the claims for another reason. The claims require that the stem or progenitor cells are cultured in serum-deprived medium. In the cited protocol, the progenitor cells are introduced into medium supplemented with TGF-β. This medium is differentiation medium. Thus, the phenotype of the cells immediately begins to change; they immediately begin to differentiate into cells of the chondroblast lineage. Thus, the stem and/or progenitor cells themselves are not actually cultured. Cells having a differentiated phenotype are cultured. For that reason as well, Applicants submit that the cited protocol does not anticipate the claims. This point is also addressed in the attached Declaration of Dr. Baksh. The Examiner is respectfully directed to that point in the Declaration on page 4.

Applicants Stand By Their Response to the Non-Final Office Action

The Examiner then repeats statements in the non-final Office Action. The Examiner refers to page 2 of that Office Action, which cites paragraph [0048]. That Office Action concludes that Baksh teaches culturing non-hematopoietic cells in serum-deprived medium. On page 3 of that Office Action, the Examiner refers to paragraphs [0063] and [0064] and then concludes "this aspect of Baksh reads on instant claim 1 wherein it cites non-static non-adherent suspension." Applicants replied to that non-final Office Action that, when Baksh teaches growth of progenitor cells, it always includes serum. On pages 5 and 6 of Applicants' reply to the non-final Office Action, Applicants explained that, throughout the Baksh application, and also in the text cited by the Examiner, Baksh does not describe progenitor cell culture that incorporates both serum-deprived medium and non-static non-adherent conditions for culturing progenitor cells. Accordingly, nothing in the Applicants' response to the non-final Office Action, with respect to the text cited in that Office Action (and, indeed, with respect to any text in the Baksh application), contradicts or is inconsistent with Applicants' discussion above or Dr. Baksh's attached Declaration.

Claim 9: Compositions

As to claim 9, the Examiner took the position that the Baksh technology would inherently produce cells with a $CD45^-/CD123^+$ phenotype. Because, for the reasons given above about how the Baksh technology is different from the presently claimed technology, the Examiner's rationale does not apply. As to the production of cell type from serum-deprived, non-static suspension culture, the Examiner is respectfully directed to the Applicants' explanation in their

reply to the non-final Office Action, particularly the paragraph spanning pages 6 and 7 of that reply. In the present Office Action, the Examiner maintains the position, notwithstanding an acknowledgement that the expansion conditions of Baksh comprise serum, while the claimed expansion conditions in the present application are serum-deprived. In maintaining the rejection of claim 9, the Examiner (on page 3 of the final Office Action) simply refers to claims 1 and 2 of the publication as follows.

> In a preferred embodiment, Baksh et al. disclose the following: "1. An enriched progenitor cell population comprising non-hematopoietic progenitor cells extractable from bone marrow, wherein the cell population is substantially devoid of at least one type of hematopoietic progenitor cells. 2. An enriched progenitor cell population according to claim 1, characterized by the absence of at least one hematopoietic progenitor cell type, wherein said cell type is one having a surface marker selected from CD3, CD14, CD39, CD45, CD66, CD119." (See claims of publication).

The Examiner then concludes that "although the expansion conditions of Baksh comprise the use of serum the isolated cell populations produced by these methods have the same characteristics as the isolated population of cells recited in instant claims 9-10." The Examiner offers no scientific rationale for this assertion and, therefore, has not met the required burden of presumption. This burden is required to meet the standards for a *prima facie* case of anticipation on the grounds of inherency, which is what the Examiner has done. The claim requires not only that the population be negative for CD45, but also that the population be positive for CD123. The above "rationale" offered by the Examiner does not address this second marker at all or provide any scientific reasoning about why one would expect that progenitor cells grown without serum in non-static conditions would lack CD45 and contain CD123.

Anticipation Cannot Be Established By Probability Or Possibility

The rejection is based on the assumption that the Baksh technology would inherently produce cells with a $CD45^-/CD123^+$ phenotype. Paragraph spanning pages 3 and 4 of the Office Action.

Applicants point out that this is unsupported speculation. The Examiner provides no scientific rationale to establish that the different culture conditions would necessarily produce the same

cells. And there is no room for speculation when establishing legal anticipation. Anticipation cannot be established by possibility or even high probability. There must be *certainty.*

The extensive body of case law in the area of anticipation under § 102 sets a black line requirement that, to anticipate a claimed invention, the prior art must disclose the claimed invention *to a certainty*. "Inherency, however, must not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Oelrich* 666 F2d. 578, 581 (CCPA 1981). This case is repeatedly cited by the Federal Circuit for this rule. As an example see *Scaltech Inc. v. Retec/Tetra LLC* 178 F3d. 1378, 1384 (Fed. Cir.1999) and *SmithKline v Apotex* 403 F.3d 1331 (Fed Cir April, 2005). In *SmithKline v Apotex*, the Federal Circuit explained that for an inherent anticipation to occur, the anticipated result must be the "inevitable result of practicing the prior art." It must "necessarily" occur.

Applied to the present case, to find anticipation would require that the conditions disclosed by Baksh would inevitably result in the claimed cells. But such a result is far from inevitable. Baksh is limited to culturing the progenitor cells in serum. Serum contains numerous cytokines. As the Examiner can appreciate, cytokines interact with cellular receptors and significantly affect gene expression. Therefore, the occurrence of cells that are $CD45^-$ and $CD123^+$ is not a certainty. For this reason alone the reference fails to anticipate the claims.
For all of these reasons, Applicants submit that the grounds for rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

B. Rejection Under 35 U.S.C. § 102(a) over Kallos

On page 4 of the Office Action, claims 1, 2, 7, 8, 11, and 13-15 are rejected under 35 U.S.C. § 102(a) on the grounds that they are anticipated by Kallos. Without acquiescing in the propriety of this rejection, Applicants point out that the rejection is moot in view of the amendment that incorporates the limitation of claim 3 into claim 1. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

C. Rejection Under 35 U.S.C. § 103(a) over Baksh in view of U.S. 6, 617, 159, herein "Cancedda"

On page 5 of the Office Action, claims 1-16 are rejected under 35 U.S.C. § 103(a) on the grounds that they are unpatentable over Baksh (above) in view of Cancedda. Applicants respectfully traverse the rejection.

On page 6 of the Office Action, the rationale for rejection is as follows.

> 12. Baksh et al. does not teach the user of a serum-free medium for the expansion of mesenchymal stem cells. However, the methods of Baksh et al. recite wherein a suitable medium for culturing non-hematopoietic cells types, including mesenchymal progenitor cells is used.
>
> 13. Cancedda et al. teach methods comprising the use of serum free media for the growth and proliferation of mesenchymal stem cells in culture. See the following embodiments of Cancedda et al. set forth on page 3 of this reference:

The explicit rationale for the rejection, found on page 7, is that Baksh teaches that the mesenchymal progenitor cells should be grown in a "suitable medium for culturing non-hematopoietic cell types" and that Cancedda teaches such a suitable medium. Accordingly, the Examiner concludes that it would have been obvious to culture stem or progenitor cells in non-static non-adherent suspension culture in the absence of serum. The Examiner's assumption is that a serum-deprived medium as taught by Cancedda would be a suitable medium for the purposes of Baksh. Applicants respectfully disagree.

To support a prima facie case of obviousness, two requirements must be met. The person of ordinary skill in the art must be motivated to make the invention and must have had a reasonable expectation that the invention could be successfully made. In the present case, neither requirement is met.

The medium described by Cancedda is suitable for expanding anchorage-dependent mesenchymal stem cells. Baksh, however, teaches expanding non-adherent mesenchymal stem cells. The effects of serum deprivation on non-adherent cells is unpredictable. The person of ordinary skill in the art would have known this. They would not have expected conditions used for adherent cells to necessarily translate to non-adherent cells. It was simply not reasonably predictable that the non-adherent cells could have been successfully expanded under conditions designed for adherent cells. Therefore, the reference would not have motivated to the person of ordinary skill in the art to make the claimed invention. And, had they

been motivated to "try" it, there would have been no reasonable expectation of success. The results were not sufficiently predictable. In the attached Declaration, Dr. Baksh explains why this is the case. The Examiner is respectfully directed to the Declaration on these points, specifically, pages 5 and 6.

In view of the above discussion and the scientific rationale in the attached Declaration, Applicants submit that the grounds for rejection have been addressed and the rejection overcome. Reconsideration and withdrawal of the rejection is, therefore, respectfully requested.

III. Conclusion

In view of the Applicants' discussion and the inventor's Declaration, Applicants believe that the pending claims are in condition for allowance. Early notification to that effect is respectfully requested. If it is believed that a further interview will expedite prosecution, the Examiner is invited to contact Applicants' attorney Adrian M. Kaplan at Heenan Blaikie LLP, at (416) 643-6972, at her convenience.

Respectfully submitted,

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